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EXAMINER	
ROBINSON, HOPE A	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/506,406	SWIERCZ ET AL.	
	Examiner	Art Unit	
	HOPE A. ROBINSON	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *3/26/08*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-24 and 26-31* is/are pending in the application.

4a) Of the above claim(s) *15-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4, 7-14,23 and 24* is/are rejected.

7)☒ Claim(s) *5,6 and 26-31* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. Applicant's response to the Office Action mailed December 26, 2007 on March 26, 2008 is acknowledged.

Claim Disposition

2. Claims 1-2, 4-24 and 26-31 are pending. Claims 1-2, 4-14, 23-24 and 26-31 are under examination.

Claim Objection

3. Claims 1-2, 4-14, 23-24 and 26-31 are objected to because of the following informalities:

For clarity and precision of claim language it is suggested that claim 1 is amended to recite "sequence identity" in lieu of "similarity" as sequence identity refers to the alignment and comparison of two or more structures. In addition, for consistency claim 1 should be amended to recite either "PAI-1 protein or PAI-1 molecule" as the claim currently recites "a molecule that is 95% similar to a PAI-1 wild type protein" (see also claims 2, 4-14, 23-24 and 26-31). For examination claim 1 is being interpreted as " A modified plasminogen activator inhibitor type -1 (PAI-1) molecule comprising a helix D, an A3 strand, an A4 strand and an A5 strand, said molecule comprising the amino acid sequence that has at least 95% sequence identity to SEQ ID NO:2, wherein SEQ ID NO:2 is modified with sulfhydryl groups such that disulfide bridges are formed

between or within said helix D region, A3 strand, A4 strand and A5 strand, and wherein said modified PAI-1 molecule has an *in vivo* half-life that is longer than the *in vivo* half-life of a corresponding wild type PAI-1 molecule".

Claim 2 is objected to because "in vivo" is not italicized (*in vivo*), hence the claim language is inconsistent with other claims.

Claim 26 is objected to for the recitation of "cl aim" and "position 10-40" in lieu of "positions 10-40", hence the claim language is inconsistent with other claims.

Claim 27 is objected to for the recitation of "position 10-40" in lieu of "positions 10-40", hence the claim language is inconsistent with other claims.

For clarity and precision of claim language is suggested that Claim 29 is amended to read "the amino acid sequence of SEQ ID NO:2" in lieu of "an amino acid sequence of SEQ ID NO:2" , hence the claim language is inconsistent with other claims.

Claims 30-31 are objected to for the recitation of "a modified PAI-1 molecule of claim 29" in lieu of "the modified PAI-1 molecule of claim 29", hence the claim language is inconsistent with other claims.

Applicant is reminded that all amendments must find support in the instant specification. Correction is required.

Maintained-Claim Rejections - 35 USC э 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-2, 4, 7-14 and 23-25 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the proteins set forth in SEQ ID NO: 2 with modifications via substitutions of sulfhydryl groups (i.e. cys and met) at specific positions, for example, does not reasonably provide enablement for any substitutions that are not sulfhydryl groups throughout SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The enablement requirement refers to the requirement that the specification describe how to make and how to use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: Quantity of Experimentation Necessary; Amount of direction or guidance presented; Presence or absence of working examples; Nature of the Invention; State of the prior art and Relative skill of those in the art; Predictability or unpredictability of the art and Breadth of the claims (see *In re Wands, 858 F.2d at 737, 8 USPQ2d at1404 (Fed. Cir. 1988*). The factors most relevant to the instant invention are discussed below.

The amount of experimentation required to practice the claimed invention is undue as the claims encompass a large variable genus of proteins and no correlation is made between structure and function with regard to the recited modifications as the claims have been amended to recite "comprising the amino acid sequence which has at least about 95% similarity to SEQ ID NO:2, in which to or more amino acid residues are each substituted…". Note that the claim language is not limited to 95% or more with the recitation of "about" and the recitation of "two or more" since "more" in association with "comprising" could be 20 or 100 amino acid residues substituted or 500 for example which means the sequence would no longer be 95% similar to SEQ ID NO:2. Further, the claims are directed to a method of treating a disease or disorder related to aberrant angiogenesis in a subject, and there is no showing of a specific disease or disorder with said product or variants of the product. Furthermore, as the claims encompass a wide variability said protein may not be effective in said treatment method.

Therefore, the claims encompass variants that may not have any biological activity. Due to the large quantity of experimentation necessary to generate the infinite number of variants recited in the claims and possibly screen same for activity and the lack of guidance/direction provided in the instant specification, this is merely an invitation to the skilled artisan to use the current invention as a starting point for further experimentation. Thus, undue experimentation would be required for a skilled artisan to make and/or use the claimed invention commensurate in scope with the claims.

Predictability of which potential changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance

with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (for example, expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, for example, multiple substitutions. In this case, the necessary guidance has not been provided in the specification. Therefore, while it is known in the art that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited, as certain positions in the sequence are critical to the protein's structure/function relationship. It is also known in the art that a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases. For example, various sites or regions directly involved in binding activity and in providing the correct three-dimensional spatial orientation of binding and active sites can be affected (see Wells, Biochemistry, vol. 29, pages 8509-8517, 1990). The instant specification provides no guidance/direction as to which regions of the protein would be tolerant of modifications and which would not, and it provides no working examples of any variant sequence that is encompassed by the claims. It is in no way predictable that randomly selected mutations, such as deletions, substitutions, additions, etc., in the disclosed sequences would result in a protein having activity comparable to the one disclosed. As plural substitutions for example are introduced, their interactions with each other and their effects on the structure and function of the

protein are unpredictable. The skilled artisan would recognize the high degree of unpredictability that all the fragments/variants encompassed in the claims would retain the recited function.

The state of the prior art provides evidence for the high degree of unpredictability as stated above. Seffernick et al. (J. Bacteriology, vol. 183, pages 2405-2410, 2001) disclose two polypeptides having 98% sequence identity and 99% sequence identity, differing at only 9 out of 475 amino acids (page 2407, right column, middle and page 2408, Fig. 3). The polypeptides of Seffernick et al. are identical along relatively long stretches of their respective sequences (page 2408, Fig. 3), however, these polypeptides exhibit distinct functions. The modifications exemplified in the Seffernick et al. reference is small compared to those contemplated and encompassed by the claimed invention.

The specification lacks adequate guidance/direction to enable a skilled artisan to practice the claimed invention commensurate in scope with the claims. Furthermore, while recombinant and mutagenesis techniques are known in the art, it is not routine in the art to screen large numbers of mutated proteins where the expectation of obtaining similar activity is unpredictable based on the instant disclosure. The amino acid sequence of a protein determines its structural and functional properties, and predictability of what mutations can be tolerated in a protein's sequence and result in certain activity, which is very complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's function from mere

sequence data are limited, therefore, the general knowledge and skill in the art is not sufficient, thus the specification needs to provide an enabling disclosure.

The working examples provided do not rectify the missing information in the instant specification pertaining to the claimed variant. The nature and properties of this claim is difficult to ascertain from the examples provided as one of skill in the art would have to engage in undue experimentation to construct the variants of the claimed invention and examine the same for function.

The specification does not provide support for the broad scope of the claims, which encompass an unspecified amount of variants of the protein and a method to prevent a disease state. The issue in this case is the breath of the claims in light of the predictability of the art as determined by the number of working examples, the skill level artisan and the guidance presented in the instant specification and the prior art of record. This make and test position is inconsistent with the decisions of *In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)* where it is stated that "...scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...". Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).*

Thus, for all these reasons, the specification is not considered to be enabling for one skilled in the art to make and use the claimed invention as the amount of experimentation required is undue, due to the broad scope of the claims, the lack of

guidance and working examples provided in the specification and the high degree of unpredictability as evidenced by the state of the prior art, attempting to construct and test variants of the claimed invention would constitute undue experimentation. Making and testing the infinite number of possible variants to find one that functions as described is undue experimentation. Therefore, applicants have not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner that reasonably correlates with the scope of the claims, to be considered enabling.

Response to Applicant's Arguments:

5. Applicant's arguments have been fully considered, however, are not completely persuasive since the rejections under 35 U.S.C. 112 first paragraph, enablement remains. Note the rejection has been amended based on the amendments made to the claims. Applicant's comments regarding the written description rejection will not be addressed herein as the rejection has been withdrawn, thus said comments are moot. Applicant's comments regarding a rejoinder of process claims, is noted.

Regarding the enablement rejection applicant states that "claims 1, 11, 12 and 13 have been amended to recite that the modified PAI-1 molecule comprises the amino acid sequence which is at least about 95% similarity to SEQ ID NO:2". Applicant's comments are noted but are not persuasive because the claims as amended are still

drawn to a large variable genus of proteins for which no correlation between function and structure is made. In claim 1 for example, the claim is drawn to a modified PAI-1 comprising a structure that is 95% similar to SEQ ID NO:2 having 2 or more amino acid substituted" and there is no limit on the amount of substitutions with the recitation of "more" in association with the open language of "comprising". Further, the language "at least about 95% similarity to SEQ ID NO:2", the structure could be 80% similar to SEQ ID NO:2" since about can be interpreted as 80%. The art acknowledges that the protein's structure-function relationship is critical to its operability, thus, modifications to the structure can result in a protein that has no function or no longer belongs to the family of PAI-1 proteins. The claims broadly recite the open language "comprising" which puts no limit on how much variability can occur in the protein's structure. The issues raised in the rejection pertain to the lack of enablement since the specification is not commensurate in scope with the claims. Applicant's comments are noted but not persuasive as the breath of the claims contemplates as much as 80 residues being varied in SEQ ID NO:2 which correspond to 80% similarity language over the 402 residues of SEQ ID NO:2. A skilled artisan would recognize the unpredictability of obtaining a structure that would retain function with this much variability any where in the structure of the protein. Thus, the rejection remains. As indicated above the claim language could be further clarified as " A modified plasminogen activator inhibitor type - 1 (PAI-1) molecule comprising a helix D, an A3 strand, an A4 strand and an A5 strand, said molecule comprising the amino acid sequence that has at least 95% sequence identity to SEQ ID NO:2, wherein SEQ ID NO:2 is modified with sulfhydryl groups such

that disulfide bridges are formed between or within said helix D region, A3 strand, A4 strand and A5 strand, and wherein said modified PAI-1 molecule has an *in vivo* half-life that is longer than the *in vivo* half-life of a corresponding wild type PAI-1 molecule".

Conclusion

6. No claims are presently allowable.

7. Applicant's amendment necessitated the new/modified ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to HOPE A. ROBINSON whose telephone number is (571)272-0957. The examiner can normally be reached on Monday-Friday 9:00-6:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat Nashed, can be reached at (571) 272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Hope A. Robinson/

Primary Examiner, Art Unit 1652